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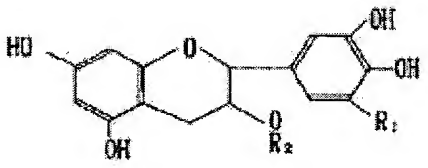
(54) SUCRASE ACTIVITY-INHIBITING AGENT

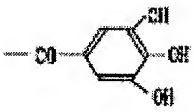
(57)Abstract:

PURPOSE: To provide a sucrase activity-inhibiting agent containing a tea polyphenol as an active ingredient and exhibiting the activity even in a small concentration without giving adverse actions on human bodies when added not only to drugs but also to foods.

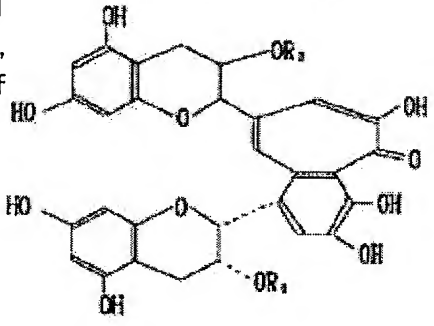
CONSTITUTION: The sucrase activity-inhibiting agent contains at least one tea polyphenol selected from a tea catechin compound of formula I (Rj1 is H, OH; R2 is H, group of formula II) and a polyphenol of formula III. The compound of formula I includes (-) epicatechin (R1=R2=H), (-) epigallocatechin (R1=OH, R2=H), (-) epicatechin gallate (R1=H, R2= group of formula II) and (-) epigallocatechin gallate (R1=OH, R2=group of formula II). The compound of formula III includes free type theaflavin (R1=R2=H), theaflavin monogallate A (R3=H, R4=group of formula II), and theaflavin monogallate B (R3 group of formula II, R4=H) and theaflavin digallate (R3=R4 group of formula II).



I



II



III

CLAIMS

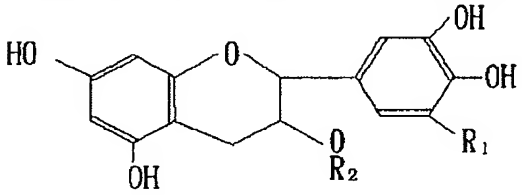
[Claim(s)]
[Claim 1]A sucrase activity inhibition agent which makes tea polyphenol an active principle.
[Claim 2]Tea polyphenol, Epigallocatechin gallate, epicatechin gallate, The sucrase activity inhibition agent according to claim 1 which are at least one sort of substances selected from epigallocatechin, epicatechin, (+) catechin and separated type theaflavin, the theaflavin mono- gallate A, the theaflavin mono- gallate B, and theaflavin digallate.

DETAILED DESCRIPTION

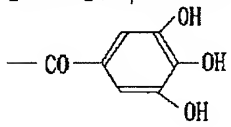
[Detailed Description of the Invention]
[0001]
[Industrial Application]At this invention, it is field-of-the-invention [of **]]. This invention relates to a sucrase activity inhibition agent, and is Shklar in detail.
Shklar who checks the activity by acting [**] for the reason.

[0002]
[Description of the Prior Art]In the present age called a "period of sumptuous lifestyle", the adult disease which accompanies obesity and it serves as a big social problem, and dietary restriction and ingestion regulation of food are important as a means of the health care. Sucrase is a digestive enzyme which exists in the human tunica mucosa intestini tenuis, and hydrolyzes sucrose into grape sugar and fructose. Therefore, obesity can be controlled, satisfying appetite moderately by checking the activity, and it is thought that there is an effect also in a diabetes-mellitus therapy. Although sucrase activity inhibition agents various now are developed, the effect is not enough and there are many in which it worries about side effects. Therefore, the activity of sucrase is checked and development of the drugs which do not have harmful side effects but can be used in comfort to a human body is desired.
[0003]
[Means for solving problem]Then, as a result of repeating research that not a chemical composition but the substance which has the drug effect made into the purpose out of a natural product should be searched, this invention person found out that this substance was contained in tea and tea polyphenol, and reached this invention.
[0004]That is, this invention provides the sucrase activity inhibition agent which uses tea polyphenol as the main ingredients.
[0005]The tea polyphenol which is the main ingredients of the sucrase activity inhibition agent of this invention is tea theaflavin expressed with the tea catechin expressed with the following general formula I, and the general formula II.

[0006]General formula I [Chemical formula 1]



[0007](R_1 shows H or OH among a formula, and R_2 is H or [Chemical formula 2].)



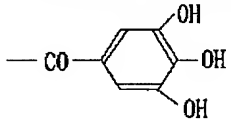
******.

[0008]There are the following as an example of tea catechin expressed with the above-mentioned general formula I.

(-) Epicatechin (the inside of the general formula I, thing of R_1=H and R_2=H)

(-) Epigallocatechin (thing of the inside of the general formula I, R_1=OH, and R_2=H)

(-) Epicatechin gallate (inside of the general formula I, R_1=H, R_2= [Chemical formula 3])



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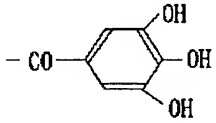
(-) Epigallocatechin gallate (the inside of the general formula I, R_1=OH, R_2= [Chemical formula 4])



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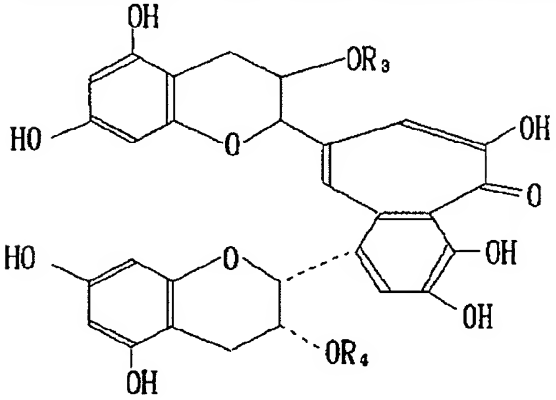
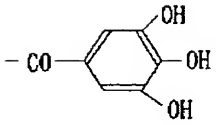
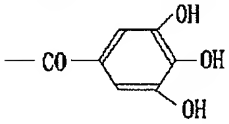
[0009]General formula II [Chemical formula 5]



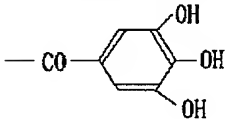
[0010](The inside of a formula, R_3, and R_4 are H or [Chemical formula 6].)



An example, R_3, and R_4 may be the same, or may differ from each other.
[0011]Next, when the theaflavin expressed with the above-mentioned general formula II is shown concretely, there are the following.
Separated type theaflavin (the inside of the general formula II, thing of R_3=H and R_4=H)
Theaflavin mono- gallate A (inside of the general formula II, R_3= [Chemical formula 7])



The thing of R_4=H
Theaflavin mono- gallate B (inside of the general formula II, R_3=H, R_4= [Chemical formula 8])



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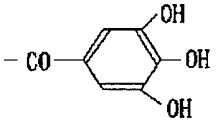
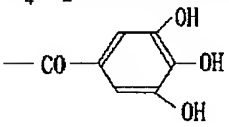
Theaflavin digallate (inside of the general formula II, R_3= [Chemical formula 9])



R_4= [Chemical formula 10]



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[0012]The above-mentioned tea polyphenol can manufacture tea leaves as a raw material, and the process is indicated in JP,S59-219384,A, a 60-13780 gazette, a 61-130285 gazette, etc.
[0013]The sucrase activity inhibition agent of this invention is used combining an excipient independent as drugs, or suitable, and also it can be added and used for foodstuffs etc. The dosage forms in the case of using this inhibitor as drugs are various, for example, the optimum dose of the tea polyphenol which is the main ingredients can be used independently, It dissolves [in solvents, such as water and alcohol,] these main ingredients furthermore and uses, or it mixes with diluents, such as excipients, such as gelatin and sodium alginate, oligosaccharide, and carboxymethyl cellulose, etc., and is used. Also when adding for foodstuffs etc., tea polyphenol can be melted and added to solvents, such as direct or water, and alcohol.
[0014]About the amount of the sucrase activity inhibition agent used of this invention,

Although what is necessary is just to determine suitably, when medicating a human body as drugs, what is necessary is just to take 0.5-10 g in taking orally so that it may become about 1-5g preferably, and the daily dose may add an excipient, a diluent, etc. as it is or suitably, may increase, and may usually take as powder medicine, a tablet, a capsule, etc. If it states from another viewpoint, the intake of the tea polyphenol which is the main ingredients will be used so that making it the concentration in the alimentary canal of a human body serve as 0.01mM - 5mM may be set to 0.1mM - 1mM desirable still more preferably.

[0015]When the sucrase activity inhibition agent of this invention is added and used for foodstuffs etc. on the other hand, for example, what is necessary is just to add so that it may obtain with bread, cereal, noodles, and rice and potato - and the quantity of this inhibitor may be 0.1 to 1.0% preferably 0.01 to 2.0% at the time of manufacture of foodstuffs, such as confectionary, such as processed products, such as a Indian millet, or a cake, a biscuit, and Cookie

[0016]

[Working example]Next, an working example explains this invention.

The sucrase of working-example 1 enzyme was prepared from the tunica mucosa intestini tenuis of the Wistar system rat based on the method (A. Dahlqvist, Anal. Biochem., 7, 18 (1964)) of Dahlqvist. Sample solution 50mul and 100micro of substrate solutions (substrate: 60mM sucrose solution) I are added to enzyme solution 50mul (221U/ml buffer solution), After making it react for 15 minutes at 37 **, the absorbance was measured for the produced reducing sugar at 540 nm by the blade FERUDO method (P. Bernfeld, Meth. Enzymol., 1, 49 (1959)). It converted into the amount of sucrose which had this value decomposed, and reaction velocity was computed based on the conventional method. On the other hand, reaction velocity at the time of adding distilled water instead of a sample solution (contrast) was made into 100% of sucrase activity, and it asked for the inhibition rate at the time of adding each sample so that it may be set to final concentration $5x10^{-4}$M. A result is shown in Table 1.

[0017]

[Table 1]

Table 1

Sample	Inhibition rate (%)
Gallic acid	6.7
(+) catechin	13.7
Epicatechin	14.7
Epigallocatechin	17.3
Epicatechin gallate	62.5
epigallocatechin-gallate	78.8
isolation type theaflavin	6.8
theaflavin mono- gallate A	45.9
theaflavin mono- gallate B	59.5
Theaflavin digallate	95.9.

[0018] Although most sucrase activity inhibition ability could not be found in epicatechin, epigallocatechin, and separated type theaflavin in the catechin shown in Table 1, and theaflavin, it was checked that other catechin and theaflavin have strong sucrase activity inhibition ability.

[0019]Divided the working-example 2 Wister system male rat (six weeks old) into two groups, one side was made to take in water (contrast), and it administered orally 1 ml of solution (80mg/(ml)) of rough catechin (trade name: the polyphenon 100, the Mitsui agriculture-and-forestry incorporated company make, and presentations are shown in Table 2.) to another side at a time, respectively. Then, the blood sugar level and the insulin concentration in blood were temporally measured with a mutarotase, the GTO method, and step enzyme immunoassay, respectively. A result is shown in drawing 1 and drawing 2.

[0020]

[Table 2]

Table 2

Presentation of polyphenon 100

constituent (tea catechin)	Ingredient ratio (%)	relative ingredient ratio (%)
GAROKATEKIN	1.44	1.6
Epigallocatechin	17.57	19.3
Catechin	-	-
Epicatechin	5.81	6.4
Epigallocatechin gallate	53.90	59.1
Epicatechin gallate	12.51	13.7
	/ 91.23	/ 100

[0021] The rise of the blood sugar level was intentionally suppressed by prescribing catechin for the patient before sucrose administration so that clearly from a figure. It was

checked that the insulin concentration in blood also serves as a low value in connection with it. The absorbed amount of sugar decreased by the sucrase inhibitory action of catechin, and it became clear from this that the blood sugar level and the insulin concentration in blood fall.

[0022]The acute toxicity test of the sucrase activity inhibition agent of working-example 3 this invention was done using the male ICR mouse. LD_{50} was computed by the Van der Waerden method. A result is shown in Table 3.

[0023]

[Table 3]

constituent	LD50 (confidence limit) mg/ml	
	oral administration	intraperitoneal administration
crude catechin*	2412	-
crude theaflavine**	-	55.2
Epigallocatechin gallate	-	150

* crude catechin constituents: see table 2

** crude theaflavine constituents: see table 4 below

[0024]

[Table 4]

Table 4

isolation theaflavin	10.0 (%)
Theaflavin mono- gallate A	22.3
theaflavin mono- gallate B	19.5
Theaflavin digallate	32.5
(+) catechin	0.3
(-)-epicatechin	1.8
(-)-epigallocatechin gallate	4.7
(-)-epigallocatechin gallate isomer	1.0
(-)-epicatechin gallate	3.9
In addition to this (theaflavin isomer etc.)	4.0

[0025]

[Effect of the Invention]In order that the sucrase activity inhibition agent of this invention may use as the main ingredients the natural product currently drunk in considerable quantities every day, even if it adds for foodstuffs from the first as drugs, there are no worries about side effects to a human body. And the sucrase activity inhibition agent of this invention checks sucrase activity by low-concentration addition. Therefore, the sucrase activity inhibition agent of this invention is very useful to sucrase activity inhibition.

[0026]

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1]Aging of the blood sugar level in the working example 2 is shown.

[Drawing 2]Aging of the insulin concentration in blood in the working example 2 is shown.

(19)日本国特許庁（ＪＰ）　(12)**公開特許公報**（Ａ）　(11)特許出願公開番号

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(43)公開日　平成５年(1993)１月26日

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Ａ６１Ｋ　31/35	ＡＤＰ	7475－4C		
	ＡＣＮ	7475－4C		
// Ｃ０７Ｄ 311/62		6701－4C		

審査請求　未請求　請求項の数２(全　８　頁)

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(22)出願日　平成３年(1991)７月３日

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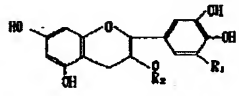
(54)【発明の名称】　シュクラーゼ活性阻害剤

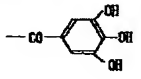
(57)【要約】　（修正有）

【構成】　下記式Ｉ及びIIの茶ポリフェノールを有効成分とするシュクラーゼ活性阻害剤。

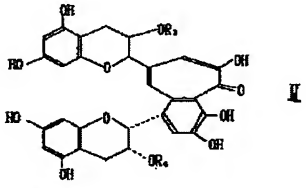


Ｉ

（式中、R_1 はＨまたはＯＨを示し、R_2 はＨまたは

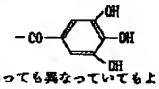


を示す。）



II

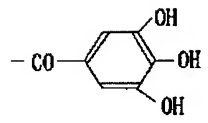
（式中、R_3 及びR_4 はＨまたは



を示し、R_3 及びR_4 は同じであっても異なっていてもよい。）

【効果】　本発明のシュクラーゼ活性阻害剤は日常相当量飲用されている天然物を主成分とするため、薬剤としてはもとより食品に添加しても人体に対する副作用の心配がなく、しかも低濃度の添加でシュクラーゼ活性を阻害する。従って、本発明のシュクラーゼ活性阻害剤はシュクラーゼ活性阻害に極めて有用である。

【化６】



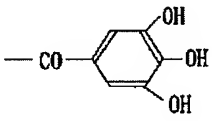
を示し、R_3 及びR_4 は同じであっても異なっていてもよい。）

【００１１】次に、上記の一般式IIで表されるテアフラビン類を具体的に示すと、以下のものがある。

遊離型テアフラビン（一般式II中、R_3 ＝H，R_4 ＝Hのもの）

テアフラビンモノガレートＡ（一般式II中、R_3 ＝

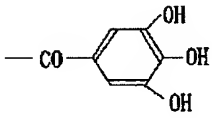
【化７】



，R_4 ＝Hのもの）

テアフラビンモノガレートＢ（一般式II中、R_3 ＝H，R_4 ＝

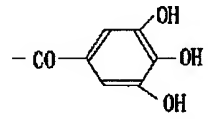
【化８】



のもの）

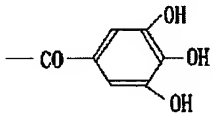
テアフラビンジガレート（一般式II中、R_3 ＝

【化９】



，R_4 ＝

【化１０】



のもの）

【００１２】上記茶ポリフェノール類は茶葉を原料として製造することができ、その製法は特開昭５９－２１９３８４号公報，同６０－１３７８０号公報，同６１－１３０２８５号公報などに記載されている。

【００１３】本発明のシュクラーゼ活性阻害剤は、薬剤として単独もしくは適当な賦形剤と組合せて用いられる他、食品等に添加して使用することができる。この阻害＊

＊剤を薬剤として使用する場合の剤形は様々であり、例えば主成分である茶ポリフェノール類の適量を単独で用いることができ、さらには該主成分を水，アルコールなどの溶媒に溶解させて用いたり、ゼラチン，アルギン酸ナトリウムなどの賦形剤、オリゴ糖，カルボキシメチルセルロースなどの希釈剤等と混合して用いられる。また、食品等に添加する場合も、茶ポリフェノール類を直接あるいは水，アルコールなどの溶媒に溶かして加えることができる。

【００１４】また、本発明のシュクラーゼ活性阻害剤の使用量に関しては、適宜決定すればよいが、薬剤として人体に投与する場合、通常は１日量が０．５～１０ｇ、好ましくは１～５ｇ程度となるように経口的に服用すればよく、そのままあるいは適宜賦形剤，希釈剤等を加えて増量し、散剤，錠剤，カプセル剤などとして服用しても良い。なお、別の観点から述べると、主成分である茶ポリフェノール類の摂取量を、人体の消化管内における濃度が０．０１ｍＭ～５ｍＭとなるようにすることが好ましく、さらに好ましくは０．１ｍＭ～１ｍＭとなるように用いる。

【００１５】一方、本発明のシュクラーゼ活性阻害剤を食品等に添加して用いる場合、例えばパン，シリアル，麺類，米・いも・とうもろこし等の加工製品あるいはケーキ，ビスケット，クッキー等の菓子類等の食品の製造時に該阻害剤の量が０．０１～２．０％、好ましくは０．１～１．０％となるように添加すれば良い。

【００１６】

【実施例】次に、本発明を実施例により説明する。

実施例１

酵素のシュクラーゼは、ウイスター系ラットの小腸粘膜より、Dahlqvist の方法（A. Dahlqvist, Anal. Biochem., 7, 18(1964)）に基づき調製した。酵素溶液５０μｌ（２２１Ｕ／ｍｌ緩衝液）に、サンプル溶液５０μｌと基質溶液（基質：６０ｍＭシュクロース溶液）１００μｌを加え、３７℃で１５分間反応させた後、生じた還元糖をベーンフェルド法(P. Bernfeld, Meth. Enzymol.,1, 49(1959))により５４０ｎｍで吸光度を測定した。この値を分解されたシュクロース量に換算し、常法に基づき反応速度を算出した。一方、サンプル溶液の代わりに蒸留水を加えた場合（対照）の反応速度をシュクラーゼ活性度１００％とし、各サンプルを終濃度5×10^{-4} Mになるように加えた場合の阻害率を求めた。結果を表１に示す。

【００１７】

【表１】

表１

サンプル	阻害率（％）

遊離テアフラビン	１０．０（％）
テアフラビンモノガレートＡ	２２．３
テアフラビンモノガレートＢ	１９．５
テアフラビンジガレート	３２．５
（＋）カテキン	０．３
（－）－エピカテキン	１．８
（－）－エピガロカテキンガレート	４．７
（－）－エピガロカテキンガレート異性体	１．０
（－）－エピカテキンガレート	３．９
その他（テアフラビン異性体等）	４．０

【００２５】

【発明の効果】本発明のシュクラーゼ活性阻害剤は日常相当量飲用されている天然物を主成分とするため、薬剤としてはもとより食品に添加しても人体に対する副作用の心配がない。しかも、本発明のシュクラーゼ活性阻害剤は低濃度の添加でシュクラーゼ活性を阻害する。従って、本発明のシュクラーゼ活性阻害剤はシュクラーゼ活＊性阻害に極めて有用である。

【００２６】

【図面の簡単な説明】

【図１】　実施例２における血糖値の経時変化を示す。

【図２】　実施例２における血中インシュリン濃度の経時変化を示す。

【図１】

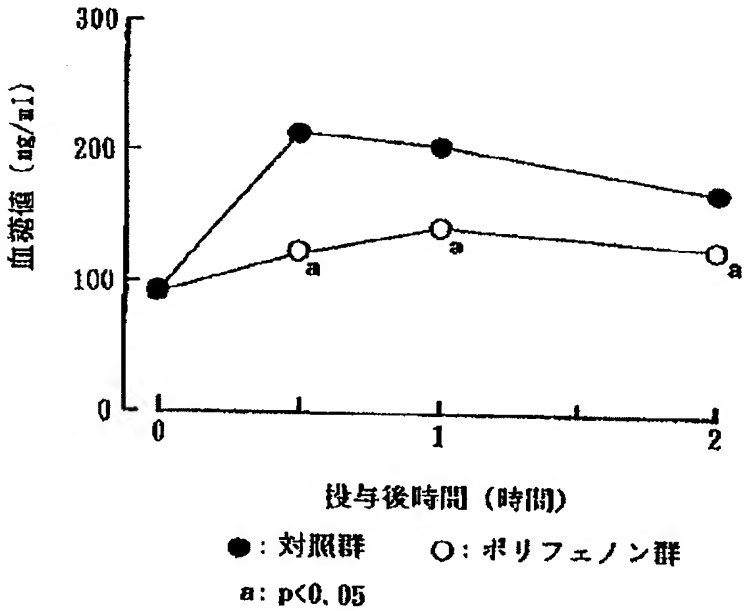


表１

サンプル	阻害率（%）
没食子酸	６．７
（＋）カテキン	１３．７
エピカテキン	１４．７
エピガロカテキン	１７．３
エピカテキンガレート	６２．５
エピガロカテキンガレート	７８．８
遊離型テアフラビン	６．８
テアフラビンモノガレートA	４５．９
テアフラビンモノガレートB	５９．５
テアフラビンジガレート	９５．９

【手続補正２】
【補正対象書類名】図面
【補正対象項目名】全図

＊【補正方法】変更
【補正内容】
＊

【図１】